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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT

PAPER NUMBER

1617

DATE MAILED: 06/28/2002

28

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/218,660

Applicant(s)

UNGER ET AL.

Examiner

Shahnam Sharareh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337 and 347-356 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 21, 27. 6) ☐ Other: _____

Continuation of Disposition of Claims: Claims pending in the application are 100,102,103,127,194-200,203,210-228,294-300,303,310-329,331-337 and 347-356.

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Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 15, 2002 has been entered.

Priority

1. Applicant's arguments with respect to the priority ruling have been fully considered and are found persuasive. The effective priority date used for the examination of the instant application is May 1, 1996.

Status of the Claims

2. Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 are pending. Applicant is requested to provide a copy of all pending claims in response to this Office Action. Any rejection that is not addressed in this Office Action is considered obviated in view of the amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider US Patent 5,643,553 (Schneider), or Grinstaff US Patent 5,498,421 (Grinstaff) in view of Wallach US Patent 4,853,228 and Allen (US Patent 5,620,689) and Ginsburg US Patent 5,656,442.

The instant claims are directed toward a formulation comprising targeted lipid vesicles comprising a gas, a linking group and a targeting ligand, wherein the linking group is a hydrophilic polymer that is covalently bound to both the surface of the lipid vesicle and

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said targeting ligand and is selected from a group consisting of PEG, polypropylene glycol, polyvinylalcohol, PVP, and copolymers thereof.

2. Schneider discloses a composition for use as an ultrasound contrast agent comprising gas-filled microbubbles, the microbubbles may contain various surfactant such as a microbubble shell forming phospholipid or more specifically PE, as well as, polymeric surfactants, such as PEG surfactants, (col 6, lines 25-64; claims 4-20).

Schneider further teaches that targeting ligands (g.g, polypeptides, antibodies, etc..) may be bound to the stabilizing surfactant layer of the microbubbles to provide site-specific targeting of the diagnostic or therapeutic microbubbles (see col 9, lines 10+).

Thus, Schneider teaches microbubbles which may comprise PE shell combined with a pIG surfactant which may be bound with a peptide targeting ligand. Schneider also teaches methods of ultrasound imaging comprising administering such liposomes compositions, see example 11. Schneider does not explicitly teach a liposome that is covalently bound to a targeting ligand via a PEG linker.

3. Grinstaff teachings are similar to those of Schneider, but the nature of the polymeric shell differs from those in Schneider. Grinstaff discloses a composition for in vivo delivery of a diagnostic or therapeutic agents comprising microbubble composition (see col 7-8). Grinstaff teaches that the polymeric shell may be modified to include suitable agents, such as phospholipid (including PE), various polymers such as polyalkylene and protein for targeting which are covalently bound to his shell, (see col 12, lines 14+). Thus, Grinstaff's microbubbles meet the limitations of the instant lipid vesicles. Grinstaff specifically teaches the conjugation of a targeting moiety to polymeric

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shell to provide advantage of site-specific delivery of the diagnostic or therapeutic microbubbles (col 8-9). Grinstaff does not explicitly teach a linker that is attached to his polymeric shell via a covalent linkage.

4. Wallace and Allen are used to show that covalent linkage between a lipid vesicle and a targeting ligand via a polymeric linker is conventional in the art. Wallace discloses a composition comprising lipid vesicles such as liposomes, which are used to the delivery of diagnostic or therapeutic agents, (see col 5, lines 8-20). Wallach also teaches that such lipid vesicles may be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site specificity, (see col 4, lines 61+). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7).

5. Allen discloses a composition comprising lipid vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shell may be formed from a phospholipid such as PE, (see entire col 6-8). Attached to the vesicle shell is a polymer chain in which a ligand (antibody) is covalently bound thereto, (see col 5-6; fig. 1, col 12, lines 29-34). Wallace and Allen do not teach gaseous liposomes or the instantly claimed targeting ligand.

Ginsberg discloses the synthetic alpha-amino acid containing chains of Lys-Gln-Ala-Gly-Asp-Val or RGD (col 33, lines 45-55) and that they specifically bind to fibrinogen of the platelet membrane glycoprotein complex IIb/IIIa receptor and that they can be used as a targeting ligand in an in vitro kit (abstract).

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Since Schneider, Grinstaff, Wallace and Allen all disclose compositins comprising targetd lipid-coated vesicles for in vivo delivery of a diagnostic or therapeutic agents, they are viewed to be in the same field of endeavor.

6. Although Schneider and Grinstaff may not specifically disclose a composition having a targeted moiety that is covalently bound to both the surface of lipid vesicles and the targeting moiety, it would have been obvious to one of ordinary skill in the art at the time of invention to modify the microbubble composition of Schneider or Grinstaff to include such a moiety because as suggested by Schneider and Grinstaff, ligands can be attached to the phospholipid walls of their lipid vesicles, and as taught by Wallace and Allen a ligand of choice, such as those taught by Ginsburg, can be attached to said lipid vesicles. The ordinary skill in the art would have performed such modifications on Schneider and Grinstaff's vesicles because he would have had a reasonable expectation of success in improving the targeting and specificity of the lipid vesicle's activity. Subsequently, methods of use and preparing such compositions would have also been obvious.

Conclusion

7. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie can be reached on 703-308-4612. The fax phone numbers

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for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

ss

June 27, 2002

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200